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Response Modification in Carcinogenesis

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A major goal in multistep carcinogenesis research is the integration of recent findings obtained by sophisticated molecular-genetic and cytogenetic analysis of cancer into the more descriptive concepts of experimental pathology. It is proposed that the creation of a promotable cell in carcinogenic initiation requires a response modification to extracellular or intercellular signals. Different types of response modification can be distinguished: changes in the receptors for growth and differentiation factors and their cytoplasmic and nuclear signal transduction pathways; increased resistance of initiated cells to cytotoxic agents; alterations in junctional cell-to-cell communications. The challenge of a response-modified cell to an appropriate promoter results in its selection and clonal expansion, usually to a benign tumor. In addition, for malignancy, chromosomal changes are required that affect cellular functions that can play a role early or late in tumorigenesis. These concepts are illustrated with examples from oncogene research and oxidant promotion.

Introduction

Over the last few years the question has arisen in carcinogenesis research of how to relate new findings obtained with sophisticated cytogenetic and molecular biological methods to the more phenomenological results of experimental pathology. Important questions are: What are the functional implications of clonal cytogenetic changes? What is the role of the activation of particular protooncogenes in multistep carcinogenesis? What is the relationship of these events to the classical concepts of multistage carcinogenesis: initiation, promotion, progression?

The stages in carcinogenesis are more readily defined by the end points that are reached than by the mechanisms and agents that accomplish the individual steps. The major result of initiation is the creation of a promotable cell. This requires a response modification to extra- or intercellular signals that distinguishes the initiated cell from the rest of the tissue. A response modification remains phenotypically unexpressed until the tissue is challenged by a promoter. The major result of promotion is the clonal expansion of the response-modified cell by a variety of mechanisms and agents that depend on the characteristics of the initiating response modification and on the tissue. In general, response modification and clonal expansion alone do not suffice for the development of a malignant tumor. Additional specific chromosomal changes are required that can occur early, before or after response modification, or later after some clonal expansion has occurred. We can speculate that response modifications in carcinogenic initiation often result from the action of mutagens, whereas chromosomal aberrations are more likely induced by clastogenic agents. It is evident that two major goals in carcinogenesis research are the characterization in functional and molecular terms of different forms of response modification and of potentially malignant chromosomal aberrations.

Promotion accomplishes the clonal expansion/selection (*1,2*) of response-modified cells by a variety of mechanisms and agents. Therefore, it is misleading to define promotion around the pharmacological properties of a specific class of promoters such as the phorbol esters. Although there may exist ideal endogenous promoters, we cannot expect to find xenobiotics that possess exclusively promoting activity. The complexity is illustrated if one considers a four-step carcinogenesis model: chromosomal alteration, response modification, promotion, progression. Six quality permutations are possible for a carcinogen that possesses two properties (e.g., a compound could be a strong clastogen plus a strong progressor, a strong clastogen plus a strong promoter, etc.).

Of course, promoters act on an entire tissue, i.e., response-modified, initiated epithelial cells, normal epithelial cells, stromal cells, inflammatory leukocytes, etc. Promoters interact with the target cells themselves or disturb short- and long-range cellular interactions. Short-range interactions may involve cell-cell communications, long-range interactions, the disturbance of paracrine signals, and the production of clastogenic factors. Individual promoters are expected to affect multiple cellular and molecular mechanisms. Only part of these may contribute to the promotional effect (but this does not mean that those other reactions are irrelevant). A better understanding of the cellular response systems to exogenous signals is a prerequisite for the unravelling of the complex pharmacology of specific xenobiotic promoters.

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Mechanisms of Response Modification Involving Changes in Signal Transduction and Gene Expression

There is much evidence from oncogene research for response modifications that involve changes in growth or differentiation factors, their receptors, and cytoplasmic and nuclear signal transduction. Several of the virally related protooncogene products are components of pathways that transmit extracellular signals to the genome (*3,4*). Candidates for protooncogenes with a potential role as response modifiers are *ras*, *src*, *tck*, *abl*, *(erbA)* with membrane or cytoplasmic functions, and *myc*, *myb*, *jun*, and *fos* with nuclear functions. The following comments focus on *ras*, *myc*, and *fos*. These examples of virally related protooncogenes were chosen because they allow mechanistic insights. Undoubtedly, additional genes with the potential to participate in response modifications remain to be identified.

The activation of a *ras* gene by a point mutation represents the prototype of a response modification. It appears to participate in the development of several forms of human cancer (*5–8*). The *ras* gene product is a 21 kD G-type protein that plays a fundamental role in membrane signal transduction (*3,9*). Not surprisingly, its activation by a point mutation can sufficiently disturb signal transduction to affect the regulation of cellular differentiation and proliferation. Indeed, there are several examples where the transfection of v-*ras* or activated c-*ras* into epithelial cells disturbed or blocked their terminal differentiation (*10–13*). In fibroblastic cells, *ras*-activation increased their sensitivity to stimulation by growth factors (*14–17*).

Changes in the expression of c-*myc* can form the basis for another type of response modification. c-*myc* codes for a nuclear protein that plays a role in DNA replication (*18–20*). Its early induction appears to be required in the recruitment of quiescent cells to competence and cell proliferation. In epithelial cells the persistent (over)expression of c-*myc* and a loss of *myc* downregulation may be incompatible with terminal differentiation (*21–24*). A lack of the responsiveness of *myc* expression to extracellular signals has been observed in premalignant and malignant cells (*25*). As was the case for *ras*, overexpression of c-*myc* in fibroblastic cells increased their response to growth factors (*17,19,26*).

The deregulation of the expression of the protooncogene c-*fos* represents a third case of response modification in carcinogenesis. c-*fos* codes for a nuclear protein that participates in the regulation of gene expression. c-*fos* is induced immediately by multiple stimuli (*27,28*). The fact that c-*fos* expression is regulated by several genetic mechanisms (*29–33*) attests to its fundamental importance in formulating at the proximal end the cellular response to extracellular signals.

The *fos* protein possesses DNA binding properties. At least in one case, the regulation of the aP2 gene in adipocyte differentiation, the binding of the *fos* protein to an upstream regulatory sequence has been directly demonstrated (*34*). Its activity is modulated by posttranslational phosphorylation (*35*) and possibly other substitution reactions.

There are several examples where a disburbance of c-*fos* expression has been observed in association with malignant transformation. In transformed, differentiation-resistant mouse epidermal cells RBK, the phorbol ester promoter TPA failed to induce c-*fos* (*25*). Similarly, active oxygen generated by xanthine/xanthine oxidase only weakly induced c-*fos* in promotable mouse epidermal cells JB6 clone 41 in contrast to the nonpromotable clone 30 (*36*).

Response Modification to Cytostatic Agents in Rat Liver Carcinogenesis

Response modification as a consequence of initiation can consist of the acquisition of increased resistance to endogenous or xenobiotic cytostatic/cytotoxic agents. In proliferating tissues the selective resistance of the response-modified cell to the cytostatic/cytotoxic promoter can suffice for clonal selection, while in nonreplicating tissues, general growth stimulation may be required in addition. The most convincing examples of response modification in the form of increased resistance to xenobiotic carcinogens derive from experimental liver carcinogenesis. In the resistant hepatocyte model of Solt and Farber (*37*), the following protocol leads to potentially malignant nodules. Treatment with an initiating carcinogen (e.g., diethylnitrosamine) is followed by the exposure to a low, noninitiating dose of a cytotoxic agent (e.g., 2-acetylaminofluorine), and growth is stimulated by partial hepatectomy or CCl_4. Other protocols related to the resistant hepatocyte model have been developed by several researchers (*38,39*). Considerable experimental evidence supports the following interpretation. Initiation has generated a rare hepatocyte with increased resistance to growth inhibition by several classes of xenobiotics or dietary deficiencies. This allows the preferential growth of initiated cells in a cytostatic/cytotoxic environment that suppresses the proliferation of the majority of hepatocytes.

Response Modification to Cytotoxic Oxidants in Mouse Skin Tumor Promotion

The evidence is convincing that oxidants and agents that induce a cellular prooxidant state can act as carcinogens, in particular as promoters and progressors (*30–46*). Bona fide oxidants with promotional activity include H_2O_2, superoxide, ozone, hyperbaric oxygen, peroxyacetic acid, chlorobenzoic acid, benzoyl peroxide, cumene hydroperoxide, *p*-nitro-perbenzoic acid, and periodate (*47,48*). Infiltrated phagocytes represent a major source of oxidants in inflamed tissues (*49, 50*), and in several in-

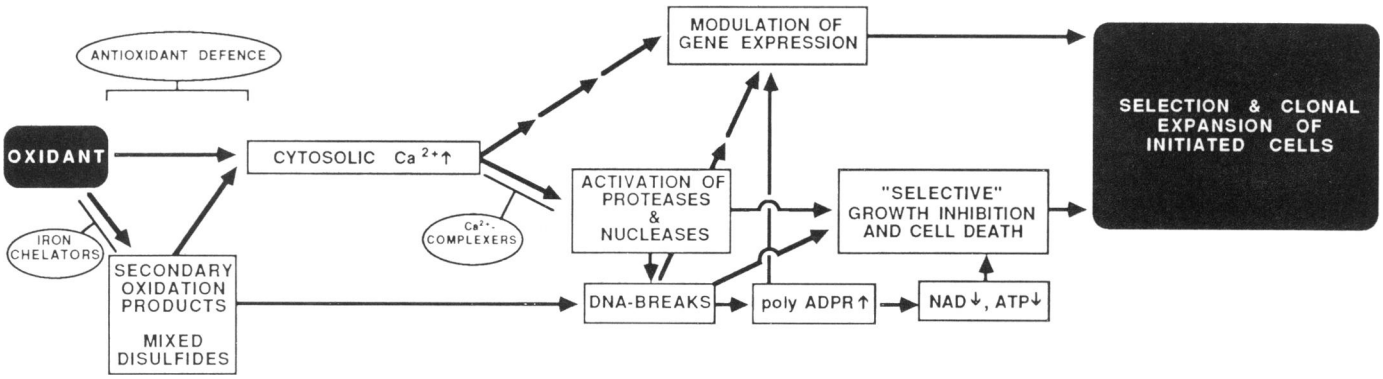

FIGURE 1. Scheme of the multiple cellular reactions that play a role in tumor promotion by extracellular oxidants.

stances inflammation appears to be a prerequisite for promotion (*51–53*). Oxidant promoters induce DNA strand breakage (*54–58*). DNA breaks elicit secondary metabolic reactions, in particular poly ADP-ribosylation of chromosomal proteins (*59*). At low oxidant concentrations, moderate levels of poly ADP-ribosylation may affect chromatin conformation and function. High oxidant concentrations may result in excessive poly ADP-ribosylation, NAD and ATP depletion, inhibition of macromolecular synthesis, and eventually cell death (*60–62*). A subtle balance between the induction of growth-related genes and cytostatic effects may have to be attained for the promotion of initiated cells by oxidants.

Our work with xanthine/xanthine oxidase as an extracellular source of active oxygen (AO) and promotable (clone 41) and nonpromotable (clone 30) mouse epidermal cells JB6 allow insights into the mechanism of action of oxidant promoters. We found that AO stimulated the growth only of promotable clone 41 after an initial period of moderate inhibition, but it was strongly cytostatic for nonpromotable clone 30. We also found that AO induced larger amounts of DNA strand breaks and poly ADP-ribosylation of chromosomal proteins in nonpromotable cells in reactions that required intracellular Fe and Ca^{2+}. Excessive DNA strand breakage and poly ADP-ribosylation may contribute to the cytostatic effect of AO (*63*). A possible reason for the differences between these two clones was discovered when we compared the constitutive levels of the activities, protein concentrations, and mRNA levels for the antioxidant enzymes catalase (CAT), Cu, Zn-superoxide dismutase (SOD), and glutathione-peroxidase (GPx). We found that CAT and SOD (but not GPx) levels were 2- to 3-fold higher in the promotable clone 41. We propose that promotable cells possess a response modification in the form of a superior antioxidant defense that protects them from excessive cytostatic effects of AO.

As exemplified by the action of polypeptide growth factors and phorbol ester promoters, growth stimulation (or arrest) requires the modulation of the expression of numerous genes. AO was capable of inducing the growth- and differentiation-related protooncogenes *fos* and *myc* in promotable and nonpromotable JB6 cells. We speculate that these genes can exert their functions only in the promotable clone 41 because the general cytostatic effects of AO are moderate (*36,63*). Our results suggest that AO may act as a mediator and activate signal transduction pathways that ultimately modulate the expression of immediate early genes such as *fos* and *myc* as do the phorbol ester TPA, serum, and certain polypeptide growth factors. Figure 1 shows a scheme of the multiple cellular reactions that play a role in tumor promotion by extracellular oxidants.

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